EXHIBIT H

1: Br J Pharmacol. 1989 Sep;98(1):318-24.

Comparison of the effects of isobutylmethylxanthine and milrinone on ischaemia-induced arrhythmias and platelet aggregation in anaesthetized rabbits.

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1. The aim of this study was to compare the effects of the non-selective phosphodiesterase (PDE) inhibitor, isobutylmethylxanthine (IBMX) and the selective PDE III inhibitor, milrinone, in a rabbit model of acute myocardial ischaemia. 2. Coronary artery occlusion caused changes in the ST-segment of the ECG and ectopic activity in all control rabbits. Ventricular fibrillation occurred in 10 out of 14 (71%) of these animals. Pretreatment with IBMX 100 micrograms kg-1 plus 10 micrograms kg-1 min-1, starting 10 min before coronary artery occlusion, reduced ischaemia-induced ST-segment changes and ventricular fibrillation occurred in only 10% of this group (n = 10). A similar dose of milrinone had no antiarrhythmic activity, whereas with a lower dose of milrinone, 30 micrograms kg-1 plus 3 micrograms kg-1 min-1 (n = 10), only 30% of rabbits fibrillated and ST-segment changes were attenuated. 3. Acute administration of both IBMX and milrinone reduced arterial blood pressure. With the higher dose of milrinone a significant effect was still present after 10 min of drug infusion. A greater hypotensive response to the higher dose of milrinone was observed in the rabbits which subsequently fibrillated during ischaemia. A marked tachycardia was also observed after administration of the higher dose of milrinone. 4. At the end of the experiment platelet aggregation was studied ex vivo. ADP-induced aggregation was reduced by pretreatment of the rabbits with milrinone but not IBMX. Both PDE inhibitors enhanced the ability of isoprenaline to inhibit ADP-induced platelet aggregation but

milrinone was more effective, particularly at the higher dose.
(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 2478245 [PubMed - indexed for MEDLINE]

PMCID: PMC1854691

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